REMARKS

Entry of the foregoing and reexamination and reconsideration of the subject application, as amended, pursuant to and consistent with 37 C.F.R. § 1.112, are respectfully requested in light of the remarks which follow.

As noted in the Office Action Summary, claims 1-57 are pending in the application. Claims 17-33, 35, 36, and 38-57 stand withdrawn. Claims 1-3 and 5-16 and 37 are amended herein. Basis for the amendments may be found throughout the specification and claims as-filed, as the amendments address and issue of spelling and recite "isolated" antibodies. No new matter is added by way of the present Amendment.

Applicants reserve the right to file at least one continuation application directed to any subject matter canceled by way of the present Amendment.

Claim Objection

Claim 37 stands objected to for an informality. Claim 37 is amended herein to replace "vaccin" with "vaccine". Thus, this objection is obviated.

Claim Rejections- 35 USC § 112, second paragraph

Claims 1-16, 34, and 37 stand rejected under 35 U.S.C. § 112, second paragraph, as purportedly indefinite, for the recitation of "derivative", as the exact meaning of the term is purportedly unclear. Applicants submit that this term is very well known to the skilled artisan. Enclosed is a copy of the definition of "derivative" taken from the Oxford dictionary of Biochemistry and Molecular Biology. Further

derivatives and derivatization is discussed in the specification, for example, at page 4, lines 3-14.

Claim 2 stands rejected for reciting "sequences are of Macaca fascicularis origin" because it is purportedly unclear if the entire sequence is from Macaca or if only the CDRs are or if only the frameworks are from Macaca. First, Applicants assume this rejection applies to claim 3, rather than claim 2, as the phrase at issue is not recited in claim 2.

Turning to the rejection, Applicants submit that this phrase recites that the CDR sequences are of Macaca fascicularis origin, and this meaning should be clear to the skilled artisan in light of both the specification as well as base claim 1. For example, page 4, lines 1-3 and page 9, lines 4-17 cite that the sequences are derived from Macaca in this regard. Claim 1, as depended upon by claim 3, refers to the CDR sequences.

Claim 1 stands rejected for the recitation of "similar unique binding properties" because it is purportedly unclear what the phrase means. Applicants submit that the meaning of this expression would be understood to the skilled artisan in light of the specification. For example, from the specification it is clear that the unique binding properties of the present invention are the capability of the antibodies to bind to a target structure displayed in, and on, the cell surface of human gastrointestinal epithelial tumor cells and in a subpopulation of normal human gastrointestinal epithelial cells, as well as a target structure displayed in or on the surface of tumor cells. To this end, Applicants refer to page 1, lines 1-9

Claim 5 is purportedly indefinite for reciting "sequences have an identify of at least 84% because it is unclear if the term "sequences" is directed to the CDRs or to

the entire antibody in claim 1. Applicants submit that the meaning of this phrase would be clear based on the specification, for example at page 4, first paragraph. Applicants further confirm that the phrase refers to how the CDR sequences have an identity of at least 84% to corresponding sequences of human origin.

Claims 11-14 stand rejected for reciting "changed" because it is purportedly unclear how the antibody has been "changed". Based on the specification, Applicants submit that it would be clear to the skilled artisan that the antibody has been genetically changed. For example, Applicants refer to page 8, line 32 to page 9, line 2 of the specification.

Claim 15 stands rejected for the recitation of "other binding structures" as it is purportedly unclear if they bind the same antigen as the unlabeled antibody. In addition, it is unclear what other binding structures having other binding specificities means. Applicants submit that this phrase is well known in the art as referring to other antibodies or binding entities.

Claim 1 stands rejected as purportedly indefinite for reciting "subpopulation of normal human gastrointestinal epithelial cells" because it is purportedly unclear what the subpopulation is. To this end, Applicants submit that the specification recites description supporting the subpopulation of cells, and provide the following comments.

As shown in the specification, A3 does not react with all epithelial cells along the gastro-intestinal tract. For example, A3 strongly reacts with epithelium of colon, but not with the esophagus. Furthermore, A3 reacted with surface epithelial cells in one of two tested samples of stomach while glandular forming epithelial cells are negative. The second sample of stomach both surface epithelium and glandular

epithelium were negative, as noted in table I and page 21 of the specification. Thus, A3 binds to a subpopulation of epithelial cells along the gastro-intestinal tract. Applicants submit that the subpopulation at issue would be understood by the skilled artisan in light of the specification.

Applicants request that the rejections under 35 U.S.C. § 112, second paragraph, be withdrawn.

Claim Rejections under 35 USC § 101

Claims 1-6, and 16 stand rejected under 35 USC § 101. In the interest of expediting prosecution, claim 1 and the antibody claims dependent on claim 1 are amended to refer to an isolated antibody. Applicants request that this rejection be withdrawn.

Claim Rejections - 35 USC § 112, first paragraph

Claims 34 and 37, stand rejected under 35 U.S.C. § 112, first paragraph, because the specification, while being enabling for a composition comprising the antibody of claim 1 which binds human gastrointestinal epithelial tumor cells and a subpopulation of normal human gastrointestinal epithelial cells or wherein the antigen is α6β4 or wherein the antibody has the six CDRs recited in claim 1, purportedly does not reasonably provide enablement for any pharmaceutical composition or any vaccine comprising the antibody of claim 1. Applicants respectfully traverse.

In order to make a rejection, the Office has the initial burden to establish a reasonable basis to question the enablement provided for the claimed invention. *In*

re Wright, 999 F.2d 1557, 1562, 27 U.S.P.Q.2d 1510, 1513 (Fed. Cir. 1993). The standard for setting forth a *prima facie* case of lack of enablement is the determination of whether the experimentation needed to practice the invention is undue or unreasonable.

In the present case, the specification, as well as what is known in the art, provide sufficient guidance for practicing the present invention within the current scope of claims 34 and 37 without undue experimentation.

The specification discloses the capacity of A3 scFV-SEA(D227A) to mediate superantigen antibody dependent cellular cytotoxicity towards Colo205 cells. Prior to the priority date of the present invention, Applicants note that it was known that the mechanism SADCC for antibody superantigen conjugates can be utilized in tumor therapy. In support, Applicants enclose an article from 1994 showing therapeutic effect of antibody superantigen conjugates in tumor therapy (Dohlsten et al., *Proc. Nat. Acad. Sci. USA,* 91:8845-8849 (1994)).

Thus, the skilled artisan would understand that the antibody according to the invention can be used as a pharmaceutical composition and as a vaccine, and also how the antibody may be used for these purposes. Determination and production of the antibodies of interest would not require undue experimentation.

Applicants respectfully request that this rejection be withdrawn.

Claim Rejections- 35 USC § 102

Claims 1, 2, 7, 8, 9, 34 and 37 stand rejected under 35 U.S.C. § 102(b) as purportedly anticipated by Fernsten et al. (*Cancer Research* 51:926-934, 1991) ("Fernsten"). The Office states that Fernsten discloses an antibody that binds

human gastrointestinal epithelial tumor cells and normal human gastrointestinal epithelial cells and the antibody is conjugated to horseradish peroxidase or 125I and compositions. Applicants traverse.

To anticipate a claimed invention under §102, a reference must teach each and every element of the claimed invention. *See Lindeman Machinenfabrik GmbH v. American Hoist and Derrick Company*, 221 USPQ 481, 485 (Fed. Cir. 1984). Fernsten does not recite each element of the present invention.

The present claims are directed to an antibody having a binding structure for a target structure displayed in, and on the cell surface of, human gastrointestinal epithelial cells. This antibody was identified in a phage library that defines selectively expressed colon cancer-associated antigens. The phage library was selected and screened on cultured tumor cells and tissue sections, and immunohistochemistry was used to identify and characterize the antibodies.

Thus, the present claims recite CDR sequences which confer unique binding properties and stucture to the antibody. The binding structures of the present antibody recognizes a non-reduced form of $\alpha 4\beta 6$ integrin as demonstrated by MALDI-TOF identification, capture ELISA and Western blot.

In contrast, Fernsten discloses a murine monoclonal antibody D612 that recognizes an antigen expressed on the cell surface of normal and malignant gastrointestinal epithelium. Unlike Fernsten, the presently claimed antibody has a unique reactivity pattern of human gastrointestinal epithelial tumor cells which supports the assertion that it is completely different to that of the monoclonal antibody D612. The antigen recognized by D612 is expressed on the cell surface of normal and malignant gastrointestinal epithelium and its estimated molecular size is

48 kDa. Further, the antibody has unusual and unexpected properties. For example, the antibody of the present invention has a unique reactivity pattern of human gastrointestinal epithelial tumor cells which is completely different to that of the monoclonal antibody D612. Furthermore, the antigen recognized by D612 is expressed on the cell surface of normal and malignant gastrointestinal epithelium and its estimated molecular size is 48 kDa, while the antigen of the present invention is of the estimated size 80 kDa – 160 kDa.

All of the above support the argument that the antibodies of the present invention are different from those of the cite reference and thus the cited reference does not recite all of the elements of the present invention.

Claims 1-2, 7, 16, 34, and 37, stand rejected under 35 U.S.C. § 102(b) purportedly as being anticipated by Quaranta et al. (U.S. Patent No. 5,320,942) ("Quaranta"). Applicants traverse.

Quaranta discloses an antigen and monoclonal antibodies having binding specificity to $\alpha 4\beta 6$ integrin. Applicants note that the present invention and Quaranta use different methodologies to produce the antibodies and therefore the resulting antibodies are also very different. The phage display technology used according to the present invention produces an antibody with selectivity between closely related structures. In contrast, monoclonal antibodies are produced against the antigen exposed to them. Therefore, different epitopes of $\alpha 4\beta 6$ integrin are recognized by the antibodies of Quaranta compared to the antibodies according to the present invention, and, thus, Quaranta does not disclose the claimed antibodies.

In light of the above, Applicants request that the rejections under 35 U.S.C. § 102 be withdrawn.

Claim Rejections- 35 USC § 103

Claims 1-2, 4-15, 34, and 37, stand rejected under 35 U.S.C. § 103(a) as purportedly unpatentable over Fernsten in view of Queen et al. (U.S. Patent No. 6,180,370) ("Queen"). Queen purportedly discloses humanized antibodies which are non-immunogenic in humans and fragments thereof and methods of producing such antibodies from hybridomas and the frameworks are human frameworks. The Office states that it would have been *prima facie* obvious to one of ordinary skill in the art to have humanized the antibody of Fernsten by the method of Queen.

To set forth a case of *prima facie* obviousness, a reference must be viewed as a whole for what it teaches; "[i]t is impermissible within the framework of section 103 to pick and choose from any one reference only so much of it as will support a given position, to the exclusion of other parts necessary to the full appreciation of what such reference fairly suggests to one of ordinary skill in the art." *In re Wesslau*, 353 F.2d 238, 241, 147 U.S.P.Q. 391, 393 (C.C.P.A. 1965); *see also Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1383, 231 U.S.P.Q. 81, 93 (Fed. Cir. 1986).

Queen discloses the production of humanized antibodies that are non-immunogenic in humans, while still retaining affinity for the antigen. Queen discloses a method of a designed strategy where CDRs from the donor Ig are grafted onto framework region from human Ig in order to produce non-immunogenic antibodies. However, unlike the present invention, this strategy does not allow the properties of

the components to be co-optimized. For example, the produced antibody is less immunogenic while the antigen is bound less tightly. In contrast, the present invention uses the phage display method, where several properties, such as target and affinity to target, of the antibody are co-optimized in the production process.

Thus, Applicants submit that there is no motivation for the skilled artisan to combine these references to achieve the claimed antibodies, as neither Fernsten nor Queen, in combination, disclose antibodies having the unique properties of the presently claimed antibodies. The reactivity patterns of the antibodies of the present invention are not shared by the antibodies taught by Fernsten and Queen.

Further, the antibodies of the present invention have different and unexpected properties as compared to the antibody taught by Fernsten. In particular, the antibody according to the present invention has a unique reactivity pattern of human gastrointestinal epithelial tumor cells which is completely different to that of the monoclonal antibody D612. Furthermore, the antigen recognized by D612 is expressed on the cell surface of normal and malignant gastrointestinal epithelium and its estimated molecular size is 48 kDa. The antigen of the present invention is of the estimated size 80 kDa – 160 kDa.

Thus, Applicants submit that the combination of Fernsten and Queen does not result in the antibodies of the present invention or provide expectation of success in obtaining same.

Claims 1-2, 4-16, 34, 37, stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Quaranta in further view of Queen. Applicants traverse.

The antibodies of Quaranta and Queen are non-immunogenic antibodies binding to the antigen $\alpha 4\beta 6$ integrin. The reactivity pattern of the antibody of Quaranta is different to the reactivity pattern disclosed by the present invention, supporting the argument that the antibodies of the cited references are not the antibodies of the present invention.

Further, the methods of producing the antibodies of the present invention are different from that of Quaranta and Queen. Applicants note that the method of producing antibodies influences what epitopes are exposed by the antigen to the antibody. Thus, different epitopes of the $\alpha 4\beta 6$ integrin will be recognized by the antibodies of the present invention and antibodies of Quaranta.

Finally, Applicants note that combining Queen with Quaranta would not result in the present invention. Queen does not disclose the phage display method of identifying novel binding structures of the present invention. No combination of the teachings by Queen and Quaranta would provide the antibodies of the present invention or an expectation of success.

Claims 1-9, 11, 14-16, 34, and 37, stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Quaranta in view of Anderson et al. (U.S. Patent No. 6,113,898) ("Anderson").

Quaranta and Anderson disclose an antibody having $\alpha 4\beta 6$ integrin as antigen. The selection and method of identification of binding structures of the present invention is different to that of Anderson. Anderson discloses a method of phage selection where the phage library is screened for antibodies abilities to bind to soluble purified human B7, B7.1 or B7.2 antigen coated plates. The identification of

binders may be determined by ELISA or radioimmunoassay. In contrast, the present invention discloses a phage display method for positive and subtractive selection of phage antibodies employing intact cells as the antigen source. As previously noted, immunohistochemistry is then applied to identify antibodies having novel and unexpected properties. Anderson does not disclose or suggest how to identify the binding structures of the present invention. Moreover, Anderson also fails to disclose to suggest how to screen for binders on whole cells which is employed by the present invention. Thus, no combination of Anderson and Quaranta discloses or provided motivation to produce the antibodies of the present invention.

Further, Applicants respectfully submit that the claims are patentable over the cited references because unexpected results are present with respect to the claimed methods.

It is a well established legal precedent that the presence of an unexpected, advantageous or superior result is evidence of nonobviousness. *See, e.g.,* M.P.E.P. § 716.02(a); *In re Papesch*, 315 F.2d 381, 137 U.S.P.Q. 43 (C.C.P.A. 1963). Along these lines, it is also well established that "a greater than expected result" is evidence of nonobviousness. *See* M.P.E.P. § 716.02(a); *In re Corkill*, 711 F.2d 1496, 226 U.S.P.Q. 1005 (Fed. Cir. 1985). The presently claimed antibodies have unique and unexpected properties. The unique immunohistochemical reactivity pattern of the present antibody shows that it recognizes several tumor types but still is able to retain low reactivity with normal human epithelial cells such as of the lung and kidney.

In light of the above remarks, Applicants request that the rejections under 35 U.S.C. § 103 be withdrawn.

CONCLUSION

From the foregoing, further and favorable action in the form of a Notice of Allowance is respectfully requested and such action is earnestly solicited.

In the event that there are any questions concerning this amendment or the application in general, the Examiner is respectfully requested to telephone the undersigned so that prosecution of the application may be expedited.

Respectfully submitted,

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